

# Automated inhaled nitric oxide alerts for adult extracorporeal membrane oxygenation patient identification

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<b>BACKGROUND:</b>	Recently, automated alerts have been used to identify patients with respiratory failure based on set criteria, which can be gleaned from the electronic medical record (EMR). Such an approach may also be useful for identifying patients with severe adult respiratory distress syndrome (ARDS) who may benefit from extracorporeal membrane oxygenation (ECMO). Inhaled nitric oxide (iNO) is a common rescue therapy for severe ARDS which can be easily tracked in the EMR, and some patients started on iNO may have indications for initiating ECMO. This case series summarizes our experience with using automated electronic alerts for ECMO team activation focused particularly on an alert triggered by the initiation of iNO.
<b>METHODS:</b>	After a brief trial evaluation, our Smart Alert system generated an automated page and e-mail alert to ECMO team members whenever a nonzero value for iNO appeared in the respiratory care section of our EMR. If iNO was initiated for severe respiratory failure, a detailed evaluation by the ECMO team determined if ECMO was indicated. For those patients managed with ECMO, we tabulated baseline characteristics, indication for ECMO, and outcomes.
<b>RESULTS:</b>	From September 2012 to July 2013, 45 iNO alerts were generated on 42 unique patients. Six patients (14%) met criteria for ECMO. Of these, four were identified exclusively by the iNO alert. At the time of the alert, the median PaO <sub>2</sub> -to-FIO <sub>2</sub> ratio was 64 mm Hg (range, 55–107 mm Hg), the median age-adjusted oxygenation index was 73 (range, 51–96), and the median Murray score was 3.4 (range, 3–3.75), indicating severe respiratory failure. Median time from iNO alert to ECMO initiation was 81 hours (range, 2–292 hours). Survival to hospital discharge was 83% in those managed with ECMO.
<b>CONCLUSION:</b>	Automated alerts may be useful for identifying patients with severe ARDS who may be ECMO candidates. ( <i>J Trauma Acute Care Surg.</i> 2014;77: S184–S189. Copyright © 2014 by Lippincott Williams & Wilkins)
<b>LEVEL OF EVIDENCE:</b>	Diagnostic test, level V.
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Despite improved understanding of the pathophysiology of adult respiratory distress syndrome (ARDS) and advancements in critical care, all-cause mortality in ARDS remains between 24% and 40%.<sup>1,2</sup> Some patients with ARDS develop severe hypoxemia refractory to mechanical ventilation (MV). It has been estimated that between 10% and 19% of these patients die as a result of their respiratory failure.<sup>3–5</sup>

In patients who fail to stabilize or improve with lung protective ventilation, various “rescue” therapies are used to improve oxygenation. These treatments can be subdivided into ventilator and nonventilator strategies<sup>5–7</sup> such as lung recruitment maneuvers,<sup>8</sup> inhaled vasodilators,<sup>9</sup> prone positioning,<sup>1</sup> and a brief period of neuromuscular blockade.<sup>10</sup> Patients who do not

respond to some or all of these measures may be considered for extracorporeal membrane oxygenation (ECMO) in specialized centers.<sup>11,12</sup>

ECMO uses a membrane lung for gas exchange in these critically ill patients with stiff, nonfunctioning lungs. Criteria for ECMO initiation in patients with severe, refractory respiratory failure are not uniform,<sup>11,13–17</sup> but for those patients who progress to ECMO, early initiation seems to be associated with improved outcomes.<sup>18–21</sup> In addition, timely consultation with experienced ECMO providers and transfer of severe ARDS patients failing conventional management may be beneficial, even if the patients are not actually placed on ECMO.<sup>11,22</sup> This principle has even been applied in combat casualties with severe respiratory failure in Iraq and Afghanistan to good effect.<sup>23,24</sup> Ultimately, to maximize the benefit of ECMO, candidate patients must be identified expeditiously.

The recent proliferation of electronic medical records (EMRs) has inspired significant advances in automated electronic health surveillance programs. We have implemented a new Smart Alert system that provides clinicians with real-time notification of critical changes in a patient’s condition gleaned from periodic processing of data items within the EMR. Others have used similar automated screening systems to identify patients at risk for acute lung injury with significantly improved sensitivity over manual patient identification and ad hoc expert consultation.<sup>25–27</sup>

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The opinions expressed in this article are solely those of the authors and do not represent an endorsement by or the views of the US Army, the US Air Force, the Department of Defense, or the US Government.

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We recently established an adult ECMO program at the San Antonio Military Medical Center (SAMMC) designed to support both our in-house patient population and those beneficiaries across the Department of Defense with severe respiratory failure including combat casualties.<sup>23</sup> We hypothesized that our Smart Alert system could be used to identify candidate ECMO patients with severe respiratory failure in our hospital. To more specifically identify patients who had failed initial ARDS interventions, we chose inhaled nitric oxide (iNO) initiation as the trigger for sending an electronic alert to the ECMO team since iNO therapy is typically used as a rescue oxygenation therapy for ARDS patients in our hospital. This series describes our early experience with iNO alerts for identifying ECMO candidates at SAMMC and details the clinical course of the initial patients managed in our ECMO program.

## PATIENTS AND METHODS

In September 2012, we began to offer ECMO therapy to adult patients ( $\geq 18$  years) with severe, refractory hypoxemia using the Extracorporeal Life Support Organization (ELSO) guidelines as a framework for ECMO initiation. Patients were identified for possible ECMO intervention by conventional physician-to-physician ECMO team consultation or by our proprietary automated electronic iNO Smart Alert. These alerts were generated by an alert engine that provides a real-time interface to Essentris EMR (CliniComp International, San Diego, CA), the inpatient EMR used at SAMMC. The Smart Alert system consists of a set of background processes (i.e. “sniffers”) that execute on a real-time view obtained from the EMR system. The iNO alert was developed to execute on an hourly basis for all patients admitted to any adult intensive care unit (ICU) within our hospital. The alert processed all respiratory parameters entered for ICU patients and matched to any nonzero iNO values within the previous 12 hours. Positive matches for initiation of iNO triggered an automated short message service text page and an e-mail to members of our ECMO team. Upon receipt of the alert, the ECMO team determined the indication for iNO (e.g., ARDS vs. pulmonary hypertension). Patients with severe respiratory failure were then evaluated in collaboration with the patient’s primary team to determine the utility of ECMO.

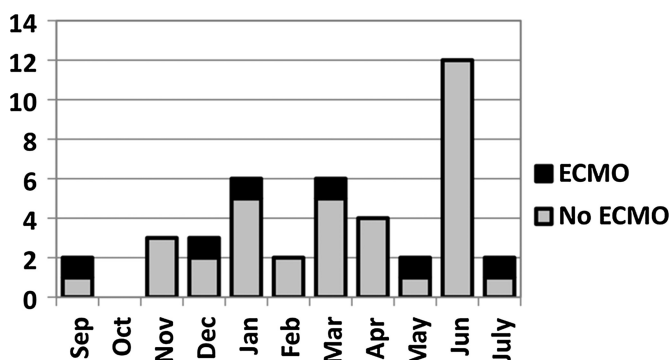
This pilot evaluation of our Smart Alert system was approved as a performance improvement project by the Brooke Army Medical Center Institutional Review Board. The total number of alerts and the indication for iNO initiation was identified. For those patients managed with ECMO, baseline characteristics were collected including age, sex, admitting diagnosis, pre-ECMO diagnosis, duration of ICU and hospital stay, and outcome. In addition, MV mode,  $\text{PaO}_2$ -to- $\text{FIO}_2$  ratio (PFR), age-adjusted oxygenation index (AOI, age + oxygenation index),<sup>28</sup> Berlin ARDS category, Murray score, duration of MV, and use of adjunct therapies were recorded for those patients at the time of the iNO alert and before the initiation of ECMO. MV mode, PFR, and AOI were recorded, when available, after 24 hours of ECMO and before termination of ECMO therapy. Summary statistics were calculated using R 3.0.2 (R Foundation, <http://www.r-project.org>). Values are reported as n (%) or median (range).

## RESULTS

During an 11-month period, a total of 45 iNO alerts were generated on 42 unique patients. All patients were evaluated by the ECMO team. Of these 42 patients, 24 (57%) had severe respiratory failure, and with the use of our current ECMO criteria, 6 (14%) were selected for ECMO therapy (Fig. 1). Alerts were also generated on 2 patients with postcardiotomy right heart failure, 10 patients with congestive heart failure or pulmonary hypertension, and 2 post-cardiac arrest patients. Four alerts were generated erroneously because of a charting error. In addition to the six patients managed with ECMO following an iNO alert, three other adult patients were managed with extracorporeal life support measures during the study period in our hospital: two patients were managed with a right ventricular assist device (RVAD) after cardiectomy, and one patient was transferred to us from Landstuhl Regional Medical Center, Germany, on ECMO for severe respiratory failure.

Summary demographics, ECMO indication, and patient disposition are shown in Table 1. Of the six evaluations resulting in ECMO initiation, four were prompted exclusively by the iNO alert. In the other cases, one evaluation was prompted by an iNO alert, which was immediately followed by a conventional consult from the medical ICU team, and the other was prompted by an intraoperative consult for severe hypoxemia in the setting of florid pulmonary edema after mitral valve replacement. At the time of iNO alert, ECMO patients had been on MV for a median duration of 9 days (range, 1–15 days). PFR was 64 mm Hg (range, 55–107 mm Hg), AOI was 73 (range, 51–96), and Murray score was 3.4 (range, 3–3.75). By the Berlin definition,<sup>29</sup> four of five patients had severe ARDS, one patient had moderate ARDS, and one patient had florid pulmonary edema with severe hypoxemia and hypercarbia. All ARDS patients had progressed to severe ARDS at the time of ECMO initiation. In addition, two patients were managed with prone positioning, and all patients were managed with neuromuscular blockade before ECMO (Table 2).

ECMO was initiated 81 hours (range, –2 hours to 292 hours) from the initial alert (Table 2). In one case, ECMO was initiated 2 hours before the alert; although iNO was initiated in the operating room, it was not charted electronically until the patient arrived in the ICU. At the time of ECMO initiation, PFR



**Figure 1.** iNO alerts on 42 unique patients from September 2012 to July 2013 shown as number of unique patients per month. Of these, six patients were managed with ECMO.

**TABLE 1.** Patient Characteristics

Patient	Age	Sex	Admitting Diagnosis	ECMO Indication	ICU Days (SAMMC Only)	Hospital Days (SAMMC Only)	Disposition (SAMMC/Other Center)
1	37	Female	TEN	ARDS	46	49	Alive
2	52	Female	Mitral regurgitation	Pulmonary edema	26	26	Alive
3	33	Female	Cystic fibrosis	ARDS	9	13	Alive/died*
4	33	Male	Fall with polytrauma	ARDS	112	180	Alive
5	35	Female	Sepsis/MRSA bacteremia	ARDS	49	56	Alive
6	19	Male	Pneumonia	ARDS	8	8	Alive/alive**
Median	34				36	38	

\*Patient survived to transfer to another facility after 13 days at SAMMC but died while awaiting lung transplantation 57 days later.

\*\*Patient was transferred to another facility after 8 days at SAMMC and survived to discharge 17 days later.

MRSA, methicillin-resistant *Staphylococcus aureus*; TEN, toxic epidermal necrolysis.

was 60 mm Hg (range, 47–80 mm Hg), AOI was 75 (range, 54–92), and Murray score was 3.6 (range, 3–4). Data were available for five patients after 24 hours of ECMO therapy. PFR increased to 98 mm Hg (range, 50–243), while AOI decreased to 56 (range, 40–79). Data were available for four patients just before the termination of ECMO therapy. Immediately before ECMO termination, PFR increased to 240 mm Hg (range, 186–372 mm Hg), and AOI decreased to 42 (range, 39–57), indicating lung recovery (Fig. 2). Median duration of ECMO therapy was 414 hours (range, 63–839 hours).

All ECMO patients survived to transfer or to discharge from SAMMC. One patient who was transferred to another facility died 57 days later while awaiting lung transplantation, while another patient transferred within 7 hours of ECMO initiation ultimately survived to discharge. Thus, five (83%) of six ECMO patients survived to final hospital discharge.

## DISCUSSION

In this case series, we present our initial experience using an automated electronic alert to identify potential adult ECMO candidates. The principal findings of this study were as follows:

(1) an iNO-based automated alert identified 24 patients with severe hypoxemia, of whom 6 were placed on ECMO; and (2) of these 6 patients, 4 were identified solely based on the alert, and in 5 patients, the ECMO team was able to be assembled semielectively before ECMO initiation. To our knowledge, this is the first description of the use of automated alerts for triggering an ECMO evaluation, and our experience establishes the feasibility of this method for identifying patients who may benefit from advanced ARDS therapies.

Automated electronic alerts have been successfully applied for the identification of patients with acute lung injury<sup>25,26,30</sup> and for early recognition of potentially injurious MV.<sup>31</sup> However, the utility of this approach specifically for ECMO consultation or initiation has never been evaluated. One challenge with using alerts for identifying potential ECMO patients is that indications for ECMO initiation vary greatly in the literature and across ECMO centers.<sup>16</sup> For example, the ELSO guidelines state that ECMO is indicated if PFR less than 80 mm Hg with FIO<sub>2</sub> greater than 0.9 and a Murray score of 3 to 4.<sup>14</sup> In contrast, the French REVA group does not recommend ECMO unless the PFR is less than 50 mm Hg despite high ventilator settings (positive end-expiratory pressure [PEEP], 10–20 cm

**TABLE 2.** Patient Characteristics at the Time of iNO Alert, Immediately Before ECMO Initiation, 24 Hours After ECMO Initiation, and Immediately Before ECMO Termination

Patient	iNO Alert to ECMO, h	MV Pre-ECMO, d	Murray Score		Berlin ARDS Category		Prone Pre-ECMO	NMB Pre-ECMO	Mode of MV				
			iNO	Pre-ECMO	iNO	Pre-ECMO			iNO Alert	Pre-ECMO	24 h	End ECMO	ECMO Duration, h
1	30	10	3	3.0	Severe	Severe	No	Yes	APRV	HFPV	HFPV	PCV	520
2	2*	1	3.75	4.0			No	Yes	AC+V	AC+V	AC+P	AC+P	63
3**	26	8	3	3.5	Severe	Severe	Yes	Yes	AC+V	AC+V	HFPV		
4	132	15	3.5	3.75	Severe	Severe	No	Yes	APRV	PCV	HFPV	PCV	839
5	292	14	3.25	3.75	Moderate	Severe	Yes	Yes	APRV	AC+V	AC+V	PCV	307
6†	154	8	3.75	3.5	Severe	Severe	No	Yes	HFOV	HFOV			
Median	81	9	3.4	3.6									414

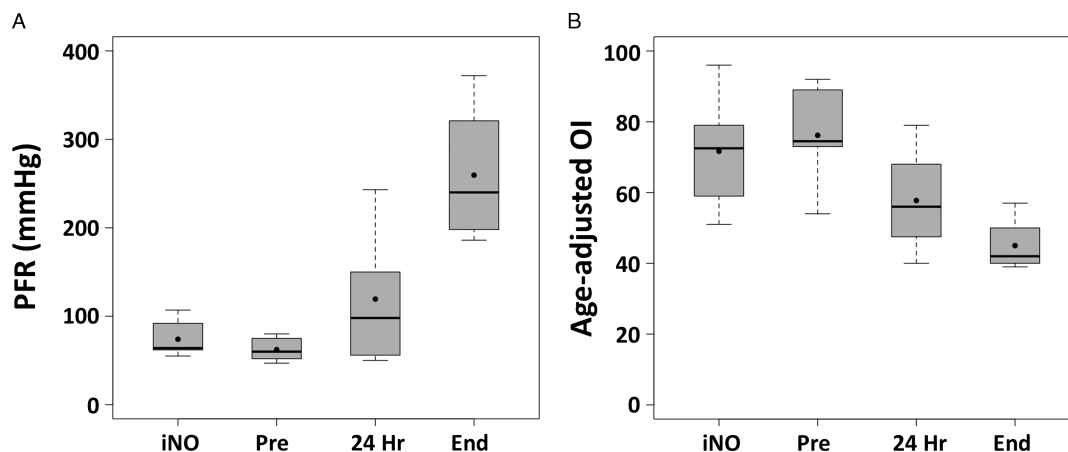
\*ECMO was initiated intraoperatively 2 hours before the iNO alert.

\*\*Patient was transferred to another facility for lung transplant evaluation.

†Patient was transferred to another facility 7 hours after ECMO initiation.

AC+P, assist control pressure.

AC+V, assist control volume; APRV, airway pressure release ventilation; HFOV, high-frequency oscillatory ventilation; HFPV, high-frequency percussive ventilation; NMB, neuromuscular blockade; PCV, pressure control ventilation.



**Figure 2.** Evolution of gas exchange characteristics in terms of PFR (A) and age-adjusted OI (B) from iNO alert (*iNO*) to immediately pre-ECMO (*Pre*) to 24 hours after ECMO initiation (*24 Hr*) and immediately before ECMO decannulation (*End*). Boxes represent the first and third quartile with the median shown as a solid line and the mean as a solid black circle inside each box. Whiskers span the maximum and minimum values.

H<sub>2</sub>O, FIO<sub>2</sub> > 0.8) or unless the plateau pressure is 35 cm H<sub>2</sub>O or greater on 4-mL/kg tidal volume.<sup>13</sup>

The indications for ECMO *evaluation* should, theoretically, be *more* inclusive than the indications for initiating ECMO. However, even this generalization does not hold true at present. On the more inclusive side, ELSO recommends considering the use of ECMO (i.e., ECMO consultation) in hypoxemic respiratory failure when PFR is less than 150 mm Hg with FIO<sub>2</sub> greater than 0.9 and/or the Murray score is 2 to 3. Similarly, during enrollment for the CESAR trial, Glenfield Hospital would initially evaluate patients with a Murray score of greater than 2.5, but the patient was not eligible for randomization unless the Murray score was 3 or greater.<sup>11</sup> In contrast, the Australian New South Wales Department of Health is more restrictive in its ECMO referral criteria<sup>15</sup> where for hypoxemic respiratory failure, immediate referral is advised for PFR less than 60 mm Hg despite optimal MV support, while a delayed referral is advised for PFR less than 100 for 48 hours.

For our ECMO program and this pilot project, we sought relatively inclusive screening criteria while trying to also avoid alert fatigue as can happen if the alert criteria are too inclusive.<sup>32</sup> Based on the ELSO guidelines<sup>14</sup> and the stepwise approach to hypoxemic respiratory failure proposed by Diaz et al.,<sup>6</sup> we initially piloted a page + e-mail alert for both a PFR/FIO<sub>2</sub>/PEEP trigger and an iNO trigger. We quickly found that the PFR/FIO<sub>2</sub>/PEEP trigger generated too many alerts, while the pattern of iNO use in our hospital resulted in a smaller number of alerts on patients with severe hypoxemic respiratory failure, pulmonary hypertension, or congestive heart failure. Thus, we set our ECMO alerts to include a page + e-mail alert when iNO was initiated and e-mail only alert if the PFR/FIO<sub>2</sub>/PEEP criteria were met. Ultimately, in our initial experience, iNO alert fatigue did not occur, as six (14%) of the patients that triggered an iNO alert went on to receive ECMO therapy and two (5%) more were managed with an RVAD. In every case that progressed to ECMO, the consult team was actively tracking the patient's response to iNO and other rescue therapies that had been applied. In several other cases, the ECMO team was

able to make useful recommendations in the management of patients, thereby avoiding the need for ECMO. To our knowledge, no patients who may have met ECMO criteria died without an ECMO team evaluation. Finally, this alert system proved useful in terms of ECMO team resource management. In five of six patients, the iNO alert permitted a decision for ECMO initiation to be made semiselectively rather than emergently.

This work represents a case series from a pilot project in the area of ECMO patient management. Although we describe a novel technique for prospective ECMO patient identification, the merits of this approach have yet to be fully evaluated. The use of iNO exclusively for identifying candidate patients for ECMO will miss several important patient populations who may benefit from extracorporeal life support (e.g., status asthmaticus with severe hypercarbia) unless they had concurrent hypoxemic respiratory failure. Regarding the clinical course of these patients, we demonstrated overall lung recovery with improved gas exchange and lung mechanics permitting ECMO decannulation in five of six cases. Although this is a very small series, early in our institutional experience, our survival rate of 83% compares favorably with the current adult survival with severe hypoxemic respiratory failure.<sup>16</sup>

There are several important potential applications of this approach. The current study applies specifically to adult patients with respiratory failure but could also be implemented in pediatric institutions that use iNO and have an EMR. Electronic alerts may also be useful for early activation of transport teams based in adult and pediatric ECMO centers within a regional civilian health system<sup>33</sup> or who are involved with long-range military transport.<sup>23</sup> In some civilian centers and the austere environment of combat, iNO is not available; however, nebulized prostacyclin has been described as an alternative, in which case the electronic sniffer could be modified to search for this parameter in the EMR instead.<sup>23,34</sup>

Future work in the use of electronic alerts for these high-risk patients should formally evaluate the time from alert to ECMO evaluation, time from alert to ECMO initiation, interventions recommended by or performed by the ECMO team,



subsequent changes in the patient's status from a respiratory standpoint, and ultimate survival as compared to or in combination with the standard system of ad hoc consultation. In addition, centers investigating ECMO indications should consider using automated alerts to avoid missing candidate patients within the participating hospitals. Finally, automated alerts should be evaluated by medical systems with an ECMO transport program to ensure both standardized referral criteria and timely ECMO team activation.

## CONCLUSION

Automated electronic iNO alerts may be useful for identifying patients with severe lung injury who may benefit from ECMO. This approach facilitates expert consultation and allows the ECMO team to assemble with advanced notice in most cases. Prospective studies evaluating the utility of electronic alerts for identification of ECMO patients are warranted.

## AUTHORSHIP

A.I.B., J.C.P., J.S., and J.W.C. designed the study. S.M.B., T.S.P., D.E.L., M.L.S. M., and J.W.C. contributed to the data acquisition. S.M.B., A.I.B., and J.W.C. performed the data analysis. A.I.B., L.C.C., K.K.C., and J.W.C. interpreted the data. S.M.B., A.I.B., and J.W.C. prepared the manuscript, which all authors critically revised.

## DISCLOSURE

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